REMARKS

Claims 1 – 20 are currently pending. Claims 1, 18, and 19 are the pending independent claims. In the Office Action, Claim 20 was rejected under Section 112, second paragraph as allegedly being indefinite. On the merits, Claims 1-17 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 4,929,605 to Domet et al. ("Domet") in combination with U.S. Patent No. 4,176,175 to Maekawa et al. ("Maekawa"). Finally, Claims 18-20 were rejected as allegedly being obvious over Domet in combination with U.S. Patent No. 6,380,381 to Obara et al. ("Obara").

Each of the foregoing rejections is respectfully traversed and favorable reconsideration is requested in view of the above amendments and following remarks.

I. The Indefiniteness Rejection.

Once again, Claim 20 was rejected for indefiniteness. Specifically the Examiner contends the claim lacks antecedent basis for the limitation "wherein the low shear mill is a conical screen mill." In response, the Applicants have herein amended Claim 20 to clarify that Claim 20 recites an additional step which is not required in Claim 19. Claim 20 now calls for the additional step of milling the dried granules using a conical screen mill. The additional step is carried out between steps (c) and (d) of Claim 19.

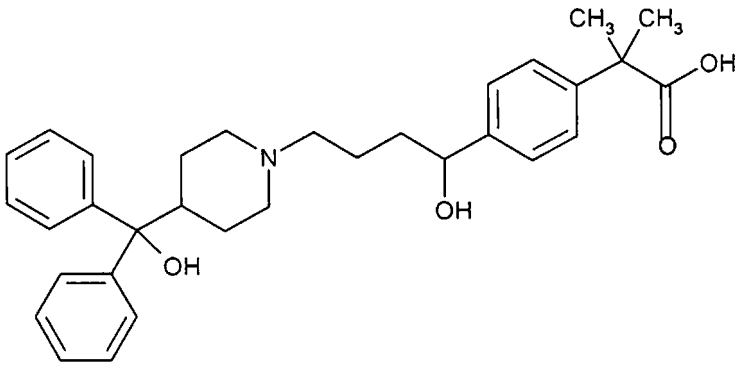
In view of this amendment, it is submitted that the indefiniteness rejection has been overcome and that the same should be withdrawn.

II. The Prior Art Rejections of Claims 1 – 17.

Claims 1-17 were rejected as allegedly being obvious over Domet in combination with Maekawa.

Independent Claim 1, and each of its dependent claims, calls for a pharmaceutical composition which consists essentially of: (1) fexofenadine or a pharmaceutical acceptable acid addition salt thereof, (2) about 10 wt. % to about 70 wt. % of lactose, and (3) about 1 wt. % to about 40 wt. % of a low-substituted hydroxypropyl cellulose.

Fexofenadine is the common name for 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-α,α-dimethylbenzeneacetic acid and may be represented by the following structural formula:



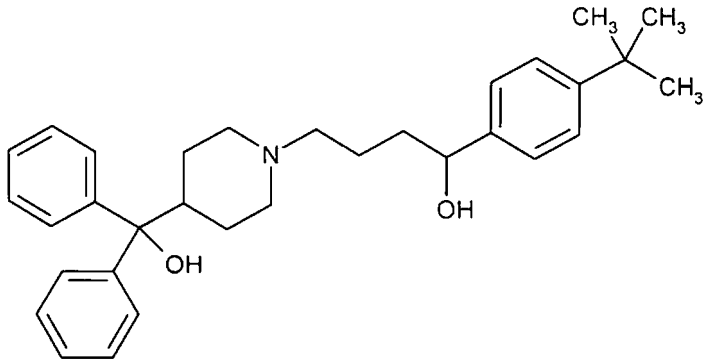
Fexofenadine

As is apparent from this structure, fexofenadine has a terminal carboxylic acid group.

The Examiner's primary reference, the Domet patent, is cited as allegedly suggesting the use of fexofenadine in a pharmaceutical composition. The Domet patent, however, fails to even mention fexofenadine. While the Domet patent does refer in general terms to piperidinoalkanol derivatives, Domet clearly and unambiguously states that

> The compound α -[4-(1,1-dimethylethyl)phenyl]-4-(hydroxydiphenylmethyl)-1-piperidinebutanol is the preferred therapeutically active ingredient.

See, Domet, Col. 3, lines 31 – 34. The common name for α -[4-(1,1-dimethylethyl)phenyl]-4-(hydroxydiphenylmethyl)-1-piperidinebutanol is terfenadine. Terfenadine may be represented by the following structural formula:



Terfenadine

Unlike fexofenadine, has terminal methyl groups rather than a terminal carboxylic acid group.

Once again, Domet makes no mention of fexofenadine. Rather Domet states that terfenadine is *the* preferred active ingredient. Further, terfenadine is used in all of the examples

disclosed in Domet. Accordingly, it is readily apparent that if one of ordinary skill in the art were being guided by the teachings of Domet in the preparation of a pharmaceutical formulation, he or she would have used terfenadine rather than fexofenadine.

As the Applicants have stressed before, terfenadine and fexofenadine have significant structural differences in that fexofenadine terminates in a carboxylic acid group while terfenadine terminates with a simple methyl group. This is not, as the Examiner suggests, a minor difference in substituent groups. This is a complete change in the functional group which terminates the molecule. One of ordinary skill would expect such a change to significantly affect the reactivity of the molecule and thus its likely pharmaceutical effectiveness. He or she would no more expect terfenadine and fexofenadine to be interchangeable with one another than he or she would expect acetic acid and ethane gas to be interchangeable with one another.

It is a long settled principle that when a reference is cited in an obviousness rejection, the reference must be taken as a whole for all that it teaches. *See In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965) ("it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.") In other words favorable teachings or suggestions in the reference may not be utilized while ignoring unfavorable portions of the reference.

Here the Domet patent, taken as a whole, would clearly lead one of ordinary skill to use terfenadine rather than fexofenadine in a pharmaceutical composition. For at least this reason, then, the cited combination of references fails to render Claim 1, and its dependent claims, obvious.

Further, even assuming arguendo, that the Domet patent might suggest the use of fexofenadine, the cited combination of the Domet and Maekawa patents still fails to suggest a pharmaceutical composition which consists essentially of: (1) fexofenadine or a pharmaceutical acceptable acid addition salt thereof, (2) about 10 wt. % to about 70 wt. % of lactose, and (3) about 1 wt. % to about 40 wt. % of a low-substituted hydroxypropyl cellulose.

In the Office Action, the Examiner concedes that the Domet patent does not suggest a composition which contains lactose and low-substituted hydroxypropyl cellulose. *See* Office Action, page 4, paragraph 1. The Examiner attempts to cure these defects with the Maekawa patent.

The Maekawa patent, however, says absolutely nothing about lactose. While Maekawa repeatedly speaks of using "sugar", the only sugar specifically referred to in Maekawa is sucrose, not lactose. Consequently, then, one of skill following the teaching of Maekawa would have been lead to use sucrose rather than lactose in any pharmaceutical composition since this was clearly Maekawa's preferred (and apparently only) embodiment.

Contrary to the Examiner's contentions, the disclosure of sucrose would not have suggested the use of lactose simply because both are disaccharides. Almost all of the common sugars are either monosaccharides or disaccharides. If, for the sake of argument, a reference to sucrose could suggest the use of other disaccharides as well, this suggestion could just as easily have led one of skill in the art to maltose or to trehalose or to cellobiose – rather than lactose. Moreover, it one of skill were seeking alternatives to sucrose, the two most logical candidates would likely be the two monosaccharides from which sucrose is made – glucose and fructose. Again, when a reference is cited in an obviousness rejection, the reference must be taken as a whole for all that it teaches. *See In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965). The Maekawa patent taken as a whole would lead one of ordinary skill to use sucrose, not lactose. The lack of any suggestion in Maekawa to use lactose and Maekawa's suggestion to use sucrose instead provides a further reason why the cited combination of Domet and Maekawa fails to suggest the composition of Claim 1.

In addition, Maekawa provides no teaching or suggestion that the sugar coating disclosed therein may be used with fexofenadine or any other form of piperidinoalkanol derivatives.

In view of these failings of the cited Domet and Maekawa references, it is respectfully submitted that their purported combination cannot fairly be said to suggest the Applicants' pharmaceutical composition as defined in independent Claim 1 and its dependent claims. Thus the obviousness rejections of these claims based upon Domet and Maekawa are improper and should be withdrawn.

III. The Prior Art Rejections of Claims 18 – 20.

Finally, Claims 18-20 were rejected as allegedly being obvious over Domet in Obara et. It is submitted that these rejections are also improper and should be withdrawn.

Independent Claims 18 and 19 are each directed to a method for preparing a pharmaceutical composition which consists essentially of (1) fexofenadine or a pharmaceutical acceptable acid addition salt thereof, (2) about 10 wt. % to about 70 wt. % of lactose, and (3)

about 1 wt. % to about 40 wt. % of a low-substituted hydroxypropyl cellulose. In both claims, the first step recited in the method is "mixing fexofenadine, lactose, and low-substituted hydroxypropyl cellulose to form a premix." This is not disclosed or suggested in Domet or Obara, either individually or taken in combination.

The failings of the Domet patent were discussed above. As the Examiner concedes, the Domet patent does not suggest a composition which contains lactose and low-substituted hydroxypropyl cellulose. Further, as previously discussed, the Domet fail also fails to teach the use of fexofenadine in a pharmaceutical composition. Instead, Domet teaches the preferred usage of terfenadine. Thus, Domet alone certainly cannot be said to suggest the step of "mixing fexofenadine, lactose, and low-substituted hydroxypropyl cellulose to form a premix."

As for the Obara patent, this reference merely discloses"low-substituted hydroxypropyl cellulose having good granulation characteristics and tablet properties." *See* Obara, Col. 1, lines 6 – 8. Obara says nothing about using this low-substituted hydroxypropyl cellulose with fexofenadine or any other form of piperidinoalkanol derivative. In fact, Obara does not specify any form of active pharmaceutical ingredient which is said to be suitable for use with the low-substituted hydroxypropyl cellulose described therein. Accordingly, Obara also fails to suggest the step of "mixing fexofenadine, lactose, and low-substituted hydroxypropyl cellulose to form a premix."

Given these individual shortcomings in the Domet and Obara references, it likewise follows that the two references cannot be combined so as to render the methods defined in Claims 18 and 19 obvious. It is therefore respectfully submitted that their purported combination cannot fairly be said to suggest the Applicants' method as defined in Claims 18 and 19 and dependent Claim 20. Thus the obviousness rejections of these claims based upon Domet and Obara are improper and should be withdrawn.

In light of the foregoing, the present the amendment is believed to place the application in a condition for allowance and entry of the foregoing amendments and allowance of Claims 1 – 20 is respectfully solicited.

In the event this response is not timely filed, Applicants hereby petition for the appropriate extension of time and request that the fee for the extension along with any other fees which may be due with respect to this paper be charged to our **Deposit Account No. 12-2355.**

Respectfully submitted,

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